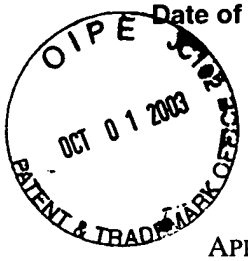
Expr ss Mail Label No.: EV 331816211US
Date of Deposit: October 1, 2003



Attorney Docket No. 00-18

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS :	Holloway *et al.*		
ASSIGNEE :	ZYMOGENETICS, INC.		
SERIAL NUMBER :	09/781,077	EXAMINER :	C. Saoud, Ph.D.
FILING DATE :	February 9, 2001	ART UNIT :	1647
FOR :	INSULIN HOMOLOG POLYPEPTIDE ZINS4		

I hereby certify that this correspondence with the enclosures listed below is being deposited with the United States Postal Service as "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Kim M. Goplen
Kim M. Goplen

October 1, 2003
Seattle, Washington

Office of Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF AMY BEATTY-YASUTAKE UNDER 37 C.F.R. §1.132

Sir:

I, Amy Beatty-Yasutake, hereby declare as follows:

1. I am employed as a Patent Paralegal in the Department of Intellectual Property & Legal Affairs of ZymoGenetics, Inc.

2. On June 19, 2003 I prepared the filing papers which accompanied the Response and Amendment under 37 C.F.R. §1.111 filed in above-identified patent application. I signed an Express Mail Certificate verifying that the Date of Deposit was June 19, 2003. I also copied the Response and Amendment under 37 C.F.R. §1.111 and the accompanying filing papers after they were completed and packaged them into an Express Mail envelope. I also affixed an Express Mail label numbered EV331815406US to the envelope and addressed the label to Commissioner for Patents, P.O. BOX 1450, Alexandria, VA, 22313. I personally handed the sealed Express Mail package to an employee of the U.S. Postal Service and I reviewed and

signed the Express Mail Pickup Service Statement. I confirmed that the Pickup Service Statement showed a "Date of Pickup" of June 19, 2003 and that it was signed by the U.S. Postal employee that picked up the package. All of these events transpired on June 19, 2003.

3. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Dated: October 1, 2003

Amy Beatty-Yasutake
c/o ZYMOGENETICS, INC.
1201 Eastlake Avenue East
Seattle, Washington 98102-3702
Tel: (206) 442-6558
Fax: (206) 442-6678

H:\Patents\Shelby\00-18\Declaration of Amy Beatty-Yasutake under 37 C.F.R.§1.132.doc

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/781,077	02/09/2001	James L. Holloway	00-18	7482

7590 08/12/2003

SHELBY J WALKER
ZYMOGENTICS INC
1201 EASTLAKE AVENUE EAST
SEATTLE, WA 98102

EXAMINER	
SAOUD, CHRISTINE J	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Exhibit A

Notice of Abandonment

Application No.	Applicant(s)
09/781,077	HOLLOWAY et al.
Examiner	**Art Unit**
Christine Saoud	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

This application is abandoned in view of:

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on *Dec 19, 2002* .

   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of ____ month(s)) which expired on _____ .

   (b) ☐ A proposed reply was received on _____ , but it does not constitute a proper reply under 37 CFR 1.113(a) to the final rejection.

   (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114).

   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).

   (d) ☒ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).

   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).

   (b) ☐ The submitted issue fee of $_____ is insufficient. A balance of $_____ is due.

   The issue fee required by 37 CFR 1.18 is $_____ . The publication fee, if required by 37 CFR 1.18(d) is $_____

   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).

   (a) ☐ Proposed new formal drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.

   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record, the assignee of the entire interest, or all of the applicants.

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34(a)) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interferences rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The reason(s) below:

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud

Petitions to revive under 37 CFR 1.137(a) or (b), or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.

21-24

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/781,077	02/09/2001	James L. Holloway	00-18	7482

7590 12/19/2002

Susan E. Lingenfelter
ZymoGenetics, Inc.
1201 Eastlake Avenue East
Seattle, WA 98102

EXAMINER
SAOUD, CHRISTINE J

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Exhibit B

Office Action Summary	Application No. 09/781,077	Applicant(s) HOLLOWAY et al.
	Examiner Christine Saoud	Art Unit 1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 15, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *31-36* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *31-36* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 8
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election without traverse of Group I in Paper No. 6 is acknowledged. Applicant's election of the species "Glu-Glu" for the affinity tag is acknowledged (paper #10).

2. Claims 1-30 have been canceled and claims 31-36 have been added as requested in the amendment of paper #7, filed 18 June 2002. Claims 31-36 are pending and under examination in the instant application.

Sequence Compliance

3. The instant specification is objected to and is not in Sequence Compliance for the following deficiencies:

At page 6 of the specification, there are nucleic acid sequences which are represented by a Sequence identifier. It is not clear if these sequence are part of a larger sequence already present in the Sequence Listing, or if they are sequences which need to be added. Regardless, these sequences must have a Sequence identifier associated with them (see 37 CFR 1.821(d)). If these sequence require the addition of Sequence identifiers to the Sequence Listing, a new paper copy and computer copy of the Sequence Listing will be required as well as a statement that the paper and computer copies are the same and include no new matter. If these nucleic acid sequences are part of a larger sequence, reference should be made to the positions and the corresponding

Sequence identifier (such as nucleotides 20-30 of SEQ ID NO:100, for example), and a new Sequence Listing would not be required. Correction is required in response to this Office action.

The amino acid sequence at page 10, line 21 (Arg-X-X-Arg) and page 38, line 25 is also encompassed by the Rules regarding nucleotide and/or amino acid sequence disclosures in Patent applications (See MPEP 2422 and 37 CFR 1.821(a)), and therefore, also requires a Sequence identifier. Correction is required in response to this Office action.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 31-36 are rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility. The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby. The instant application does not disclose the biological role of this protein/DNA or its significance.

It is clear from the instant specification that the "insulin homolog polypeptide Zins4" described therein is what is termed an "orphan protein" in the art. This is a protein whose cDNA has been isolated because of its similarity to known proteins; in the instant case, similarity to

relaxin and insulin. There is little doubt that, after complete characterization, this protein may be found to have a specific, substantial and credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to a protein (and compositions thereof) of as yet undetermined function or biological significance. It is clear, based on amino acid sequence similarity, that the protein of the claimed invention is evolutionarily related to insulin and relaxin, and therefore a new member of the insulin/relaxin family. However, this family of proteins is divergent in function and therefore, there is no well-established utility for the family members based on amino

acid sequence identity alone. The biological activities of insulin are very different from those of relaxin (see Straus, Endocrine Rev. 5(2): 356-369, 1984 and Bryant-Greenwood et al., Endocrine Rev. 15(1): 5-26, 1994), although the proteins are clearly of similar structure (see Bryant-Greenwood, Endocrine Rev. 3(1): 62-90, 1982). A sequence comparison of the claimed protein reveals approximately 50% amino acid identity to both insulin and relaxin family members (percentages differ depending on the protein of the family). Therefore, there is as much structural similarity to insulin as there is to relaxin, and one of ordinary skill in the art would not know if the biological activities of relaxin or insulin will be possessed, or if the protein will have its own distinct biological activity. The instant specification asserts that the claimed polypeptide may be used for pregnancy support (page 42 of the specification, for enhancing fertilization during assisted reproduction (page 42), for treating reproductive disorders (page 43), for treatment of disorders associated with gonadal development, pregnancy, pubertal changes, menopause, ovarian cancer, fertility, ovarian function, polycystic ovarian syndrome and other reproductive functions, modulation/treatment/prevention of pathological conditions in ovary, as well as suppression or control of ovulation for birth control (page 43, paragraph 2-3). The specification further asserts use of the claimed invention for diagnostic methods to analyze reproductive function or evaluation of ovarian cancer (page 43, bottom). Additionally, the specification asserts that the claimed polypeptide may modulate contractility in certain tissues and may be use for treatment of cardiovascular disease, infertility, *in vitro* fertilization, birth control, treating impotence or other male reproductive dysfunction, as well as inducing birth (see page 44, paragraph 1).

There is absolutely no evidence of record or any line of reasoning that would support the asserted uses or biological activities asserted in the instant specification. Furthermore, there is absolutely no evidence of record or any line of reasoning that would support a conclusion that the claimed polypeptide and compositions can be used in any method of treatment as implied in the specification, because it is not known what conditions/disorders/diseases would be responsive to the claimed invention, if any, because no biological activity has been disclosed for the claimed invention. Until some actual and specific significance can be attributed to the claimed protein of SEQ ID NO:2, the instant invention is incomplete. The disclosure that the claimed invention shares sequence similarity with relaxin and insulin is not a disclosure of how to use the claimed invention because the proteins which the claimed invention is related to have distinct biological activities and could not be used in the same manner. Furthermore, the biological activity or significance of the claimed invention cannot be predicted based on amino acid sequence information alone because the class of compounds to which the instant invention is related has divergent biological activities. In the absence of a knowledge of the biological activity or significance of the claimed invention, there is no immediately obvious patentable use for it. To employ the polypeptide of the instant invention in any of the disclosed methods would clearly be using it as the object of further research which has been determined by the courts to be a utility which, alone, does not support patentability. Since the instant specification does not disclose a credible "real world" use for claimed polypeptide and compositions thereof, then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. §101 as being useful.

6. Claims 31-36 are rejected under 35 U.S.C. §112, first paragraph, as failing to adequately teach how to use the instant invention for those reasons given above with regard to the rejection of these claims under 35 U.S.C. §101.

Conclusion

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Christine J. Saoud, Ph.D., whose telephone number is (703) 305-7519. The Examiner can normally be reached on Monday to Thursday from 8AM to 2PM. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. §§ 1.6(d) and 1.8). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternate number. Official papers filed After Final rejection filed by fax should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud

FORM PTO 1449 (REV 2-32)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	File No. 00-18	Serial No. 09/781,077
	INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)	Applicant(s): James L. Holloway *et al.*	
		Filing Date: February 9, 2001	Group: 1647

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Patents, etc.)

	A1		International Search Report for application No. PCT/US01/04199.
	A2		DOE Joint Genome Institute, "Sequencing of Human Chromosome 19," Accession No. AC022098 (January 27, 2000).
	A3		Bathgate RA, Samuel CS, Burazin TC, *et al.*, "Human relaxin gene 3 (H3) and the equivalent mouse relaxin (M3 gene," *Journal of Biological Chemistry 277(2)*:1148-1157 (January 11, 2002).

Examiner	Date considered

EXAMINER: Initial if citation considered, whether or not citation is in conformance with M.P.E.P. 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Notice of References Cited	Application/Control No. 09/781,077	Applicant(s)/Patent Under Reexam HOLLOWAY et al.	
	Examiner Christine Saoud	Art Unit 1647	Page 1 of 1

U.S. PATENT DOCUMENTS

		Document Number Country Code-Number-Kind Code	Date MM-YYYY[1]	Name	Classification[2]	
	A					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

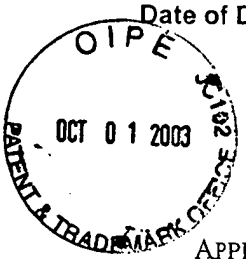
		Document Number Country Code-Number-Kind Code	Date MM-YYYY[1]	Country	Name	Classification[2]	
	N						
	O						
	P						
	Q						
	R						
	S						
	T						

NON-PATENT DOCUMENTS

		Include, as applicable: Author, Title, Date, Publisher, Edition or Volume, Pertinent Pages
	U	Bryant-Greenwood et al. Endocrine Reviews. 15(1): 5-26, 1994.
	V	Bryant-Greenwood et al. Endocrine Reviews. 3(1): 62-90, 1982.
	W	Straus. Endocrine Reviews. 5(2): 356-369, 1984.
	X	

* A copy of this reference is not being furnished with this Office action. See MPEP § 707.05(a). [1] Dates in MM-YYYY format are publication dates. [2] Classifications may be U.S. or foreign.

Express Mail Label No.: EV33[illegible]15406US
Date of Deposit: June 19, 2003



Attorney Docket No. 00-18

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS :	Holloway *et al.*		
ASSIGNEE :	ZYMOGENETICS, INC.		
SERIAL NUMBER :	09/781,077	EXAMINER :	C. Saoud, Ph.D.
FILING DATE :	February 9, 2001	ART UNIT :	1647
FOR :	INSULIN HOMOLOG POLYPEPTIDE ZINS4		

I hereby certify that this correspondence with the enclosures listed below is being deposited with the United States Postal Service as "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Amy Beatty-Yasutake
Amy Beatty-Yasutake

June 19, 2003
Seattle, Washington

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE

This paper is in response to the Office Action mailed December 19, 2002, and is due on June 19, 2003 with a three (3) month extension of time. Accordingly, Applicants enclose herewith the appropriate response, a Petition for a three (3) month extension of time pursuant to 37 C.F.R §1.136(a) and the required fee under 37 C.F.R. §1.17(c). However, the Commissioner is hereby authorized to charge any fee due with this submission, or credit any overpayment of same, to Deposit Account No. 26-0290; Reference No. 00-18.

In response to the Office Action mailed December 19, 2002, please amend the above-identified application as follows:

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of the claims, which begins on page 4 of this paper.

Remarks/Arguments begin on page 11 of this paper.

[redacted]

Exhibit C

Amendments to the Specification:

Please replace the paragraph beginning at pg. 6, line 16, with the following amended paragraph:

The term "complements of a polynucleotide molecule" denotes a polynucleotide molecule having a complementary base sequence and reverse orientation as compared to a reference sequence.

Please replace the paragraph beginning at pg. 6, line 20, with the following amended paragraph:

The term "contig" denotes a polynucleotide that has a contiguous stretch of identical or complementary sequence to another polynucleotide. Contiguous sequences are said to "overlap" a given stretch of polynucleotide sequence either in their entirety or along a partial stretch of the polynucleotide.

Please replace the paragraph beginning at pg. 10, line 7, with the following amended paragraph:

Processing of the protein involves cleavage at the C-terminus of the signal peptide, and, based on predicted structural homology with other mature members of the insulin family, a cleavage at the C-terminus of the B chain and at the N-terminus of the A chain, resulting in removal of the C-peptide. Analysis of the zins4 polypeptide of SEQ ID NO:2 with other known members of the insulin family suggests a signal peptide cleavage site in the region of amino acid residue 25 (Ala) of SEQ ID NO:2. Cleavage at the C-terminus of the B chain is predicted to be at the C-terminal of amino acid residue 53 (Arg) or residue 54 (Arg) followed by cleavage of the Arg residues by carboxypeptidase to leave amino acid residue 52 (Trp) as the C-terminal amino acid residue. Cleavage sites resulting in the N-terminus of the A chain are suggested in the region of amino acid residue 115 (Arg) to 118 (Arg). Cleavage is predicted to be after the C-terminus of amino acid residue 118 (Arg) leaving amino acid residue 119 (Asp) as the N-terminal amino acid residue of the A chain. The C-terminal amino acid is residue 142 (Cys). The cleavage site at the

junction of the C-peptide and A chain is highly conserved, occurring after Arg-X-X-Arg (SEQ ID NO:13; wherein X is any amino acid residue), Arg-Arg or Lys-Arg; however, the cleavage sites at the junction of the signal sequence and B chain, and at the junction of the B chain and C-peptide, do not maintain a similarly high degree of conservation within the insulin family.

Listing of the Claims:

Claims 1 through 36 (cancelled).

37. (New claim) An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) an amino acid sequence from residue 1 (Met) to residue 25 (Ala) of SEQ ID NO:2;

(b) an amino acid sequence from residue 1 (Met) to residue 52 (Trp) of SEQ ID NO:2;

(c) an amino acid sequence from residue 1 (Met) to residue 118 (Arg) of SEQ ID NO:2;

(d) an amino acid sequence from residue 1 (Met) to residue 142 (Cys) of SEQ ID NO:2;

(e) an amino acid sequence from residue 26 (Arg) to residue 52 (Trp) of SEQ ID NO:2;

(f) an amino acid sequence from residue 26 (Arg) to residue 53 (Arg) of SEQ ID NO:2;

(g) an amino acid sequence from residue 26 (Arg) to residue 54 (Arg) of SEQ ID NO:2;

(h) an amino acid sequence from residue 26 (Arg) to residue 114 (Leu) of SEQ ID NO:2;

(i) an amino acid sequence from residue 26 (Arg) to residue 118 (Arg) of SEQ ID NO:2;

(j) an amino acid sequence from residue 34 (Leu) to residue 47 (Cys) of SEQ ID NO:2;

(k) an amino acid sequence from residue 37 (Arg) to residue 41 (Arg) of SEQ ID NO:2;

(l) an amino acid sequence from residue 55 (Ser) to residue 114 (Leu) of SEQ ID NO:2;

(m) an amino acid sequence from residue 55 (Ser) to residue 115 (Arg) of SEQ ID NO:2;

(n) an amino acid sequence from residue 55 (Ser) to residue 116 (Gly) of SEQ ID NO:2;

(o) an amino acid sequence from residue 55 (Ser) to residue 117 (Ser) of SEQ ID NO:2;

(p) an amino acid sequence from residue 55 (Ser) to residue 118 (Arg) of SEQ ID NO:2;

(q) an amino acid sequence from residue 55 (Ser) to residue 142 (Cys) of SEQ ID NO:2;

(r) an amino acid sequence from residue 115 (Arg) to residue 142 (Cys) of SEQ ID NO:2;

(s) an amino acid sequence from residue 116 (Gly) to residue 142 (Cys) of SEQ ID NO:2;

(t) an amino acid sequence from residue 117 (Ser) to residue 142 (Cys) of SEQ ID NO:2;

(u) an amino acid sequence from residue 118 (Arg) to residue 142 (Cys) of SEQ ID NO:2;

(v) an amino acid sequence from residue 119 (Asp) to residue 142 (Cys) of SEQ ID NO:2; and

(w) an amino acid sequence from residue 128(Cys) to residue 142 (Cys) of SEQ ID NO:2.

38. (New claim) The isolated polypeptide of claim 37, further comprising an affinity tag.

39. (New claim) The isolated polypeptide of claim 38, wherein the affinity tag is selected from the group consisting of: poly-histidine tract, protein A, glutathione S transferase, Glu-Glu affinity tag, substance P, Flag peptide, streptavidin binding peptide, maltose-binding protein, and an immunoglobulin domain.

40. (New claim) An isolated polypeptide consisting of an amino acid sequence selected from the group consisting of:

(a) an amino acid sequence from residue 1 (Met) to residue 25 (Ala) of SEQ ID NO:2;

(b) an amino acid sequence from residue 1 (Met) to residue 52 (Trp) of SEQ ID NO:2;

(c) an amino acid sequence from residue 1 (Met) to residue 118 (Arg) of SEQ ID NO:2;

(d) an amino acid sequence from residue 1 (Met) to residue 142 (Cys) of SEQ ID NO:2;

(e) an amino acid sequence from residue 26 (Arg) to residue 52 (Trp) of SEQ ID NO:2;

(f) an amino acid sequence from residue 26 (Arg) to residue 53 (Arg) of SEQ ID NO:2;

(g) an amino acid sequence from residue 26 (Arg) to residue 54 (Arg) of SEQ ID NO:2;

(h) an amino acid sequence from residue 26 (Arg) to residue 114 (Leu) of SEQ ID NO:2;

(i) an amino acid sequence from residue 26 (Arg) to residue 118 (Arg) of SEQ ID NO:2;

(j) an amino acid sequence from residue 34 (Leu) to residue 47 (Cys) of SEQ ID NO:2;

(k) an amino acid sequence from residue 37 (Arg) to residue 41 (Arg) of SEQ ID NO:2;

(l) an amino acid sequence from residue 55 (Ser) to residue 114 (Leu) of SEQ ID NO:2;

(m) an amino acid sequence from residue 55 (Ser) to residue 115 (Arg) of SEQ ID NO:2;

(n) an amino acid sequence from residue 55 (Ser) to residue 116 (Gly) of SEQ ID NO:2;

(o) an amino acid sequence from residue 55 (Ser) to residue 117 (Ser) of SEQ ID NO:2;

(p) an amino acid sequence from residue 55 (Ser) to residue 118 (Arg) of SEQ ID NO:2;

(q) an amino acid sequence from residue 55 (Ser) to residue 142 (Cys) of SEQ ID NO:2;

(r) an amino acid sequence from residue 115 (Arg) to residue 142 (Cys) of SEQ ID NO:2;

(s) an amino acid sequence from residue 116 (Gly) to residue 142 (Cys) of SEQ ID NO:2;

(t) an amino acid sequence from residue 117 (Ser) to residue 142 (Cys) of SEQ ID NO:2;

(u) an amino acid sequence from residue 118 (Arg) to residue 142 (Cys) of SEQ ID NO:2;

(v) an amino acid sequence from residue 119 (Asp) to residue 142 (Cys) of SEQ ID NO:2; and

(w) an amino acid sequence from residue 128(Cys) to residue 142 (Cys) of SEQ ID NO:2.

41. (New claim) An isolated polypeptide comprising SEQ ID NO:2.

42. (New claim) The isolated polypeptide of claim 41, further comprising an affinity tag.

43. (New claim) The isolated polypeptide of claim 42, wherein the affinity tag is selected from the group consisting of: poly-histidine tract, protein A, glutathione S transferase, Glu-Glu affinity tag, substance P, Flag peptide, streptavidin binding peptide, maltose-binding protein, and an immunoglobulin domain.

44. (New claim) An isolated polypeptide consisting of SEQ ID NO:2.

45. (New claim) An isolated polypeptide comprising:

(a) a B chain comprising amino acid sequence selected from the group consisting of:

(i) an amino acid sequence from residue 26 (Arg) to residue 52 (Trp) of SEQ ID NO:2,

(ii) an amino acid sequence from residue 26 (Arg) to residue 53 (Arg) of SEQ ID NO:2,

(iii) an amino acid sequence from residue 26 (Arg) to residue 54 (Arg) of SEQ ID NO:2,

(iv) an amino acid sequence from residue 34 (Leu) to residue 47 (Cys) of SEQ ID NO:2, and

(v) an amino acid sequence from residue 37 (Arg) to residue 41 (Arg) of SEQ ID NO:2; and

(b) a C peptide comprising an amino acid sequence selected from the group consisting of:

(i) an amino acid sequence from residue 55 (Ser) to residue 114 (Leu) of SEQ ID NO:2,

(ii) an amino acid sequence from residue 55 (Ser) to residue 115 (Arg) of SEQ ID NO:2,

(iii) an amino acid sequence from residue 55 (Ser) to residue 116 (Gly) of SEQ ID NO:2,

(iv) an amino acid sequence from residue 55 (Ser) to residue 117 (Ser) of SEQ ID NO:2, and

(v) an amino acid sequence from residue 55 (Ser) to residue 118 (Arg) of SEQ ID NO:2; and

(c) an A chain comprising an amino acid sequence selected from the group consisting of:

(i) an amino acid sequence from residue 115 (Arg) to residue 142 (Cys) of SEQ ID NO:2,

(ii) an amino acid sequence from residue 116 (Gly) to residue 142 (Cys) of SEQ ID NO:2,

(iii) an amino acid sequence from residue 117 (Ser) to residue 142 (Cys) of SEQ ID NO:2,

(iv) an amino acid sequence from residue 118 (Arg) to residue 142 (Cys) of SEQ ID NO:2,

(v) an amino acid sequence from residue 119 (Asp) to residue 142 (Cys) of SEQ ID NO:2, and

(vi) an amino acid sequence from residue 128(Cys) to residue 142 (Cys) of SEQ ID NO:2,

wherein the B chain, C peptide and A chain are joined by inter- and intra-chain disulfide bonds.

46. (New claim) The isolated polypeptide of claim 45, wherein the B chain comprises an an amino acid sequence from residue 26 (Arg) to residue 52 (Trp) of SEQ ID NO:2, the C peptide comprises an amino acid sequence from residue 55 (Ser) to residue 114 (Leu) of SEQ ID NO:2, and the A chain comprises an amino acid sequence from residue 119 (Asp) to residue 142 (Cys) of SEQ ID NO:2.

47. (New claim) The isolated polypeptide of claim 45, further comprising an affinity tag.

48. (New claim) The isolated polypeptide of claim 47, wherein said affinity tag is selected from the group consisting of: poly-histidine tract, protein A, glutathione S transferase, Glu-Glu affinity tag, substance P, Flag peptide, streptavidin binding peptide, maltose-binding protein, and an immunoglobulin domain.

49. (New claim) An isolated polypeptide comprising:

(a) a B chain comprising amino acid sequence selected from the group consisting of:

(i) an amino acid sequence from residue 26 (Arg) to residue 52 (Trp) of SEQ ID NO:2,

(ii) an amino acid sequence from residue 26 (Arg) to residue 53 (Arg) of SEQ ID NO:2,

(iii) an amino acid sequence from residue 26 (Arg) to residue 54 (Arg) of SEQ ID NO:2,

(iv) an amino acid sequence from residue 34 (Leu) to residue 47 (Cys) of SEQ ID NO:2, and

(v) an amino acid sequence from residue 37 (Arg) to residue 41 (Arg) of SEQ ID NO:2; and

(b) an A chain comprising an amino acid sequence selected from the group consisting of:

(i) an amino acid sequence from residue 115 (Arg) to residue 142 (Cys) of SEQ ID NO:2,

(ii) an amino acid sequence from residue 116 (Gly) to residue 142 (Cys) of SEQ ID NO:2,

(iii) an amino acid sequence from residue 117 (Ser) to residue 142 (Cys) of SEQ ID NO:2,

(iv) an amino acid sequence from residue 118 (Arg) to residue 142 (Cys) of SEQ ID NO:2,

(v) an amino acid sequence from residue 119 (Asp) to residue 142 (Cys) of SEQ ID NO:2, and

(vi) an amino acid sequence from residue 128(Cys) to residue 142 (Cys) of SEQ ID NO:2,

wherein the B chain and A chain are joined by inter- and intra-chain disulfide bonds.

50. (New claim) The isolated protein of claim 49, wherein the B chain comprises an an amino acid sequence from residue 26 (Arg) to residue 52 (Trp) of SEQ ID NO:2, and the A chain comprises an amino acid sequence from residue 119 (Asp) to residue 142 (Cys) of SEQ ID NO:2.

51. (New claim) The isolated protein of claim 45, further comprising an affinity tag.

52. (New claim) The isolated protein of claim 51, wherein said affinity tag is selected from the group consisting of: poly-histidine tract, protein A, glutathione S transferase, Glu-Glu affinity tag, substance P, Flag peptide, streptavidin binding peptide, maltose-binding protein, and an immunoglobulin domain.

53. (New claim) A composition, comprising a pharmaceutically acceptable carrier and a polypeptide of claim 37.

54. (New claim) A composition, comprising a pharmaceutically acceptable carrier and a polypeptide of claim 41.

55. (New claim) A composition, comprising a pharmaceutically acceptable carrier and a polypeptide of claim 45.

56. (New claim) A composition, comprising a pharmaceutically acceptable carrier and a polypeptide of claim 49.

Remarks

Upon entry of the foregoing amendments, claims 37 – 56 are under consideration. Applicants have cancelled claims 31 – 36 and added new claims 37 – 56 to more clearly define the present invention. New claims 37 – 56 are directed to polypeptides based on SEQ ID NO:2 in general. More particularly, new claims 37 – 56 are directed to structural elements within the polypeptides of the present invention. Specifically, new claims 37 – 44 are directed to structural elements with Zins4, including the B chain, C peptide and the A chain. New claims 45 – 52 are directed to polypeptides which comprising the B chain, C peptide and A chain, as well as polypeptides which only contain the B chain and the A chain. New claims 53 – 56 are directed to compositions comprising a pharmaceutically acceptable carrier and the polypeptides of the present invention. Basis for these new claims can be found in the Specification as originally filed, and specifically in original claims 1 – 8 and 30, and at pg. 2, lines 13-19; pg. 3, lines 1-20; pg. 10, lines 7-28; and pg. 11, lines 5-11.

Applicants have amended the Specification at pg. 6 to remove the nucleic acid sequences used as examples of either a hypothetical "complementary sequence" or a hypothetical "contig" as they neither encompass the present invention nor are necessary to practice the present invention. Applicants have amended the Specification at pg. 10 to include a sequence identifier for the amino acid sequence Arg-X-X-Arg.

The present amendments add no new matter.

SEQUENCE COMPLIANCE

The Examiner has objected to the Specification as not being in compliance with the Sequence Rules under 37 C.F.R. §1.821(d).

Applicants have amended the Specification at pg. 6 to remove the nucleic acid sequences used as examples of either a hypothetical "complementary sequence" or a hypothetical "contig." These sequences were merely included as an exemplification of each term. These sequences are not necessary to practice the present invention.

Applicants have amended the Specification at pg. 10 to include identify the amino acid sequence Arg-X-X-Arg as SEQ ID NO:13. Applicants file concurrently herewith a replacement Sequence Listing in compliance with the Sequence Rules under 37 C.F.R. §1.821(d). The replacement Sequence Listing reflects the addition of new SEQ ID NO:13, as described above.

Accordingly, Applicants believe that the present objections are now moot.

THE §101 REJECTION

The Examiner has rejected claims 31 – 36 under 35 U.S.C. §101, alleging that the claimed invention has no apparent or disclosed specific and substantial credible utility, as the instant application does not disclose the biological role of the claimed protein/DNA or its significance.

Applicants traverse. Applicants respectfully submit that the rejection is contrary to both the law and the United States Patent Office's own examination guidelines. The application of these standards to biotechnology inventions is discussed in the January 5, 2001 Utility Examination Guidelines, which state:

> An invention has a well-established utility if a person of ordinary skill would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties...), and the utility is specific, substantial, and credible...

See e.g. Utility Examination Guidelines, 66 F.R. 4 at pg. 1098, §II.B.1(c)(1). Moreover, "[a] patent examiner must accept a utility asserted by an applicant unless the Office has sound scientific reasoning to rebut the assertion." *Id.*

Structural similarity with a compound that has a known therapeutic or pharmacological utility is routinely found to be indicative of a well-established utility and supportive of an assertion of therapeutic utility for a similar compound. *See e.g.*, M.P.E.P. 2107.03; *see also*, In re Jolles, 628 F.2d 1322, 206 U.S.P.Q. 885 (CCPA 1980). And, as discussed in detail in the January 5, 2001 Federal Register Notice of the United States Patent

Office's Utility Examination Guidelines:

> When a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein. . . . [A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient.

See e.g. Utility Examination Guidelines, 66 F.R. 4 at pg. 1096.

Applicants contend that the Office has not established a *prima facie* showing of lack of utility, nor provided sound scientific reasoning to rebut the assertion of utility in the application. As detailed below, one of skill in the art upon reading the specification would appreciate that the Zins4 polypeptides of the present invention are useful because Zins4 is a member of the relaxin superfamily.

As stated in the Specification, the polypeptides of the present invention have "homology to the relaxin family." *See e.g.* Specification at pg. 9, lines 13-15. Specifically, these polypeptides share **numerous structural similarities** with the hormone relaxin. For instance, the polypeptides of the present invention contain a B chain-C peptide-A chain motif found in the relaxins. *Id* at pg. 9, line 36 through pg. 10, line 1. More specifically, the polypeptides of the present invention share a classical relaxin structure, known as the "cysteine motif," which is highly conserved in the B and A chains of relaxin. *Id* at pg. 9, lines 27-35. In fact, "[s]equence analysis indicates that the human polypeptide sequence (SEQ ID NO:2) is **structurally equivalent** to other members of the [relaxin] family." *Id* at pg. 10, lines 5-6. Further, the length of the B chain, C peptide and A chain correspond closely to those of relaxin itself. *Id* at pg. 10, line 7 through pg. 11, line 15. Most importantly, the polypeptides of the present invention contain a R-x-x-x-R-x-x-I motif in the middle of the B-chain (starting at amino acid residue 37 (Arg) through residue 44 (Ile) of SEQ ID NO:2). This motif has been determined to be "**essential for relaxin receptor binding.**" *See e.g.*, Bathgate *et al.*, *J. Bio. Chem.* 227:2 1148-1157 (2001) (cited in the June 12, 2002 Information Disclosure Statement as reference "A3") (*emphasis added*); *see also*, Specification at pg. 9, lines 31-35. In fact, Zins4 and relaxin *alone* share this B chain motif. These structural characteristics are well known in the art and are recognized as defining and directing relaxin's biological function(s). The presence of these

structural similarities would lead one of ordinary skill in the art to conclude that the polypeptides of the present invention are closely related to relaxin and consequently are more likely than not to have a substantially similar biological function as relaxin.

Furthermore, relaxin has a well-known and established biological function and many well-known utilities generally associated with female reproductive tract physiology. *See e.g.*, Bathgate *et al.*, *J. Bio. Chem.* 227:2 1148-1157 (2001). Specifically, relaxin has been shown to have utility in its ability to inhibit myometrial contractions, to stimulate remodeling of the connective tissue and to induce softening of the tissues of the birth canal. *Id* at pg. 1148. Relaxin has also demonstrated utility by its ability to breakdown of collagen, one of the main components of connective tissue. *Id.*

And, as acknowledged by the Examiner in her December 19, 2002 Office Action, Applicants have asserted a number of utilities which directly related to Zins4 application in female reproductive tract physiology, including contractility of tissues such as myometrial. *See e.g.* Specification at pg. 44, lines 13-37. Thus, one skilled in the art, in light of Zins4 obvious homology to relaxin, would immediately recognize and appreciate that the polypeptides of the present invention are useful in the same manner that relaxin itself is useful. Accordingly, one skilled in the art would immediately recognize the polypeptides of the present invention have a "real world use" that is specific, substantial and credible.

The Examiner has stated that the "instant claims are drawn to a protein (and compositions thereof) of as yet undetermined function or biological significance" and consequently, the "instant specification does not disclose a credible 'real world' use. *See e.g.,* December 19, 2002 Office Action at pg. 4.

Applicants disagree. Zins4 does indeed have an established and recognized biological function and significance. As discussed in detail above, Applicants have disclosed a biological function(s) for the polypeptides of the present invention. The presence of the disclosed structural similarities of Zins4 and relaxin would lead one of ordinary skill in the art to conclude that the polypeptides of the present invention are part of the relaxin family of proteins and consequently are more likely than not to share relaxin's well-known biological function(s). Furthermore, Bathgate *et al.* further substantiated the biological function of Zins4. Specifically, they used the

identical polypeptide, designated as "*H3* relaxin," which is disclosed in the present application as Zins4 (SEQ ID NO:2) to determine biological function of the polypeptide:

> Therefore, our data provide conclusive evidence that this novel peptide retains the structural features necessary for interaction with, and activation of, relaxin receptors and can therefore be termed a "relaxin."

See e.g., Bathgate *et al.* at pg. 1156.

Applicants assert that the polypeptides of the present invention would be recognized by one skilled in the art as having actual and specific significance. Applicants also assert that one skilled in the art would immediately recognize that the polypeptides of the present invention have a well-known biological function based on the surrounding art and the structural similarities of these polypeptides to relaxin. Thus, Applicants assert that the present Application does indeed disclose a credible "real world" use for the claimed polypeptides.

Based on the foregoing, it is clear that Examiner's assertions that the "claimed invention has no apparent or disclosed specific and substantial credible utility", as the instant application "does not disclose the biological role of the claimed protein/DNA or its significance" are unfounded. New claims 37 – 56 are indeed supported by a well-established and specific and substantial credible utility as described above. This is more than 35 U.S.C. §101 requires. The Office has not established a *prima facie* showing of lack of utility, nor sound scientific reasoning to rebut the assertions of utility in the application. Consequently, Applicants request that the Examiner withdraw the present rejection under 35 U.S.C. §101.

THE §112, FIRST PARAGRAPH REJECTION

The Examiner has rejected claims 31 – 36 under 35 U.S.C. §112, first paragraph, alleging that the Specification fails "to adequately teach how to use the instant invention for those reasons given above with regard to the rejection of these claims under 35 U.S.C.

Applicants traverse. Applicants have indeed taught how to use the instant invention. As discussed above, Applicants have shown that the polypeptides of the present invention share numerous structural similarities with relaxin and, in fact, have been classified by those skilled in the art as being relaxins. Consequently, Applicants have shown a biological activity for the

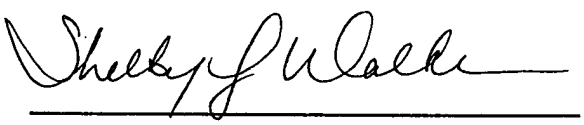
polypeptides of the present invention. Thus, Applicants assert that the Specification more than adequately teaches how to use the present invention.

Accordingly, Applicants maintain that they have indeed asserted a specific and substantial credible utility and well-established utility for the claimed polypeptides. The Zins4 polypeptides of the present invention are useful, and therefore one of skill in the art could make and use the invention. Consequently, Applicants request that the Examiner withdraw the rejection of claim 11 under 35 U.S.C. §112, first paragraph.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If for any reason the Examiner feels that a telephone conference would expedite prosecution of the Application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



Dated: June 19, 2003

Shelby J. Walker, Reg. No. 45,192
Attorney for Applicants
c/o ZYMOGENETICS, INC.
1201 Eastlake Avenue East
Seattle, Washington 98102-3702
Tel: (206) 442-6558
Fax: (206) 442-6678

Enclosures:
Petition and Fee for Extension of Time (in duplicate)
Amendment Fee Transmittal (in duplicate)
Postcard

H:\Patents\Shelby\00-18\Response to the December 19, 2002 Office Action.doc

PATENT APPLICATION
File No: 00-18

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	James L. Holloway, Si Lok, Stephen R. Jaspers
Serial No.	:	09/781,077
Group Art Unit	:	1647
Examiner	:	Saoud, C.
Filed	:	February 9, 2001
For	:	INSULIN HOMOLOG POLYPEPTIDE ZINS4
Date Submitted	:	June 19, 2003

PETITION AND FEE FOR EXTENSION OF TIME (37 C.F.R. 1.136(a))

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

It is respectfully requested that the time for response to the Office Action dated December 19, 2003 be extended for a period of three months from March 19, 2003 to June 19, 2003.

Applicants claim small entity status. Please charge the total fee, estimated to be $465.00, to ZymoGenetics, Inc., Deposit Account No. 26-0290. A duplicate of this sheet is enclosed.

Respectfully submitted,

Shelby J. Walker
Registration No. 45,192

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AMENDMENT FEE TRANSMITTAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith is an Amendment for the above-mentioned application. The fee required to be filed with the accompanying amendment has been calculated as shown below:

CLAIMS AS AMENDED

	Claims Remaining After Amendment	Highest No. Covered by Previous Payments	Present Extra	Extra Rate	Fee
Total	20	-30	0	$9.00	$000.00
Independent	6	-8	0	$42.00	$000.00
1st Presentation of Multiple Dependent Claim				$140.00	$000.00
				Total	$000.00

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Applicants : James L. Holloway, Si Lok, Stephen R. Jaspers
USSN : 09/781,077
Filed : February 9, 2001
For : INSULIN HOMOLOG POLYPEPTIDE ZINS4

The USPTO hereby acknowledges receipt of the following:
1. Amendment and Certificate of Mailing (16 pages)
2. Amendment Fee Transmittal (in duplicate)
3. Petition and Fee for Extension of Time (in duplicate)

Via Express Mail Label No. EV331815406US on June 19, 2003

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ZYMOGENETICS INC
1201 EASTLAKE AVE E
SEATTLE WA 98102-3702

00-18 Amend.
ABY

TO: (PLEASE PRINT) PHONE ( )
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Exhibit D

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1. Attach Meter Strip or Stamps Here 00-18

2. Customer Name and Address (No., Street, Suite No., City, and State)

ZYMOGENETICS INC
1201 EASTLAKE AVE E
SEATTLE WA 98102-3702

ZIP + 4 9 5 1 0 2 3 7 0 2

3.

Express Mail	Quantity
Priority Mail	Quantity
Parcel Post	Quantity

4. Custom Design Agreement

CDA No.

5. Method of Payment

☐ Corporate Account No.
☐ Federal Agency Account No.
☐ Meter Strip or Stamps (Apply fee in Item 1 above)

6. Express Mail Label Numbers

Item No.	Express Mail Label Number	Item No.	Express Mail Label Number	Item No.	Express Mail Label Number
1	EV331915410 6 US	6		11	
2		7		12	
3		8		13	
4		9		14	
5		10		15	

7. Customer Signature	8a. USPS Signature	8b. Date of Pickup	8c. Time of Pickup

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Delivery Date Mo. Day	Time ☐ AM ☐ PM	Employee Signature

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NO DELIVERY ☐ Weekend ☐ Holiday

Customer Signature

CUSTOMER USE ONLY

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FROM: (PLEASE PRINT) PHONE ( )

ZYMOGENETICS INC
1201 EASTLAKE AVE E
SEATTLE WA 98102-3702

00-18 Amend

TO: (PLEASE PRINT) PHONE ( )

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PO BOX 1450
ALEXANDRIA VA 22313-1450

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EMS

File No. : 00-18
Applicants : James L. Holloway, Si Lok, Stephen R. Jaspers
USSN : 09/781,077
Filed : February 9, 2001
For : INSULIN HOMOLOG POLYPEPTIDE ZINS4

The USPTO hereby acknowledges receipt of the following:

1. Amendment and Certificate of Mailing (16 pages)
2. Amendment Fee Transmittal (in duplicate)
3. Petition and Fee for Extension of Time (in duplicate)

Via Express Mail Label No. EV331815406US on June 19, 2003

Attorney Docket No. 00-18

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS :	Holloway *et al.*		
ASSIGNEE :	ZYMOGENETICS, INC.		
SERIAL NUMBER :	09/781,077	EXAMINER :	C. Saoud, Ph.D.
FILING DATE :	February 9, 2001	ART UNIT :	1647
FOR :	INSULIN HOMOLOG POLYPEPTIDE ZINS4		

I hereby certify that this correspondence with the enclosures listed below is being deposited with the United States Postal Service as First Class Mail on the date indicated below and is addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: amy Beatty-Yasutake
Amy Beatty-Yasutake

August 11, 2003
Seattle, Washington

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL AMENDMENT

This paper is supplemental to the response to the Office Action mailed December 19, 2002. The Commissioner is hereby authorized to charge any fee due with this submission, or credit any overpayment of same, to Deposit Account No. 26-0290; Reference No. 00-18.

Remarks

In Applicants' response mailed June 19, 2003, Applicants inadvertently failed to enclose the replacement sequence listing referred to in the Remarks.

Applicants enclose herewith a replacement Sequence Listing in compliance with the Sequence Rules under 37 C.F.R. §1.821(d). The replacement Sequence Listing reflects the addition of new SEQ ID NO:13, as described above.

The content of the paper and computer readable copies are the same and, where applicable, includes no new matter, as required by 37 CFR 1.821-1.825.

CONCLUSION

Applicants respectfully submit that the pending claims are in condition for allowance. If for any reason the Examiner feels that a telephone conference would expedite prosecution of the Application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

Dated: August 11, 2003

Shelby J. Walker, Reg. No. 45,192
Attorney for Applicants
c/o ZYMOGENETICS, INC.
1201 Eastlake Avenue East
Seattle, Washington 98102-3702
Tel: (206) 442-6558
Fax: (206) 442-6678

Enclosures:
Paper Copy of Sequence Listing (6 sheets)
Sequence Listing Diskette
Postcard

PATENT APPLICATION
File No: 00-18

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	James L. Holloway, Si Lok, Stephen R. Jaspers
Serial No.	:	09/781,077
Group Art Unit	:	1647
Examiner	:	Saoud, C.
Filed	:	February 9, 2001
For	:	INSULIN HOMOLOG POLYPEPTIDE ZINS4
Date Submitted	:	August 11, 2003

AMENDMENT FEE TRANSMITTAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith is a Supplemental Amendment for the above-mentioned application. The fee required to be filed with the accompanying amendment has been calculated as shown below:

CLAIMS AS AMENDED

	Claims Remaining After Amendment	**Highest No. Covered by Previous Payments**	**Present Extra**	**Extra Rate**	**Fee**
Total	20	-30	0	$9.00	$000.00
Independent	6	-8	0	$42.00	$000.00
1st Presentation of Multiple Dependent Claim				$140.00	$000.00
				Total	$000.00

Applicants claim small entity status. Please charge any required fee to ZymoGenetics, Inc., Deposit Account No. 26-0290. A duplicate of this sheet is enclosed.

Respectfully submitted,

Shelby J. Walker
Registration No. 45,192

PATENT APPLICATION
File No: 00-18

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	James L. Holloway, Si Lok, Stephen R. Jaspers
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Respectfully submitted,

Shelby J. Walker
Registration No. 45,192

SEQUENCE LISTING

<110> Holloway, James L.
Lok, Si
Jaspers, Stephen R.

<120> Insulin Homolog Polypeptide Zins4

<130> 00-18

<150> US 60/188,544
<151> 2000-03-10

<160> 13

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 429
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(429)

<400> 1

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Met Ala Arg Tyr Met Leu Leu Leu Leu Ala Val Trp Val Leu Thr
 1               5                  10                  15

ggg gag ctg tgg ccg gga gct gag gcc cgg gca gcg cct tac ggg gtc       96
Gly Glu Leu Trp Pro Gly Ala Glu Ala Arg Ala Ala Pro Tyr Gly Val
            20                  25                  30

agg ctt tgc ggc cga gaa ttc atc cga gca gtc atc ttc acc tgc ggg      144
Arg Leu Cys Gly Arg Glu Phe Ile Arg Ala Val Ile Phe Thr Cys Gly
        35                  40                  45

ggc tcc cgg tgg aga cga tca gac atc ctg gcc cac gag gct atg gga      192
Gly Ser Arg Trp Arg Arg Ser Asp Ile Leu Ala His Glu Ala Met Gly
    50                  55                  60
```

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gat acc ttc ccg gat gca gat gct gat gaa gac agt ctg gca ggc gag      240
Asp Thr Phe Pro Asp Ala Asp Ala Asp Glu Asp Ser Leu Ala Gly Glu
 65                  70                  75                  80

ctg gat gag gcc atg ggg tcc agc gag tgg ctg gcc ctg acc aag tca      288
Leu Asp Glu Ala Met Gly Ser Ser Glu Trp Leu Ala Leu Thr Lys Ser
                85                  90                  95

ccc cag gcc ttt tac agg ggg cga ccc agc tgg caa gga acc cct ggg      336
Pro Gln Ala Phe Tyr Arg Gly Arg Pro Ser Trp Gln Gly Thr Pro Gly
            100                 105                 110

gtt ctt cgg ggc agc cga gat gtc ctg gct ggc ctt tcc agc agc tgc      384
Val Leu Arg Gly Ser Arg Asp Val Leu Ala Gly Leu Ser Ser Ser Cys
        115                 120                 125

tgc aag tgg ggg tgt agc aaa agt gaa atc agt agc ctt tgc tag          429
Cys Lys Trp Gly Cys Ser Lys Ser Glu Ile Ser Ser Leu Cys  *
    130                 135                 140
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<210> 2
<211> 142
<212> PRT
<213> Homo sapiens

<400> 2

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 1               5                  10                  15
Gly Glu Leu Trp Pro Gly Ala Glu Ala Arg Ala Ala Pro Tyr Gly Val
            20                  25                  30
Arg Leu Cys Gly Arg Glu Phe Ile Arg Ala Val Ile Phe Thr Cys Gly
        35                  40                  45
Gly Ser Arg Trp Arg Arg Ser Asp Ile Leu Ala His Glu Ala Met Gly
    50                  55                  60
Asp Thr Phe Pro Asp Ala Asp Ala Asp Glu Asp Ser Leu Ala Gly Glu
65                  70                  75                  80
Leu Asp Glu Ala Met Gly Ser Ser Glu Trp Leu Ala Leu Thr Lys Ser
                85                  90                  95
Pro Gln Ala Phe Tyr Arg Gly Arg Pro Ser Trp Gln Gly Thr Pro Gly
            100                 105                 110
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Val Leu Arg Gly Ser Arg Asp Val Leu Ala Gly Leu Ser Ser Ser Cys
115 120 125
Cys Lys Trp Gly Cys Ser Lys Ser Glu Ile Ser Ser Leu Cys
130 135 140

<210> 3
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Cysteine motif

<221> VARIANT
<222> (3)...(13)
<223> Each Xaa is independently any amino acid residue
except cysteine.

<400> 3
Leu Cys Gly Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
1 5 10

<210> 4
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Motif

<221> VARIANT
<222> (3)...(5)
<223> Each Xaa is independently any amino acid resdiue
except cysteine.

<221> VARIANT
<222> (4)...(14)
<223> Each Xaa is independently any amino acid residue
except cysteine.

<400> 4

Cys Cys Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
1 5 10 15

<210> 5
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Motif

<221> VARIANT
<222> (2)...(4)
<223> Each Xaa is independently any amino acid residue except cysteine.

<400> 5
Arg Xaa Xaa Xaa Arg
1 5

<210> 6
<211> 426
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate polynucleotide sequence encoding the polypeptide of SEQ ID NO:2.

<221> variation
<222> (1)...(426)
<223> Each N is independently A, T, G, or C.

<400> 6
atggcnmgnt ayatgytnyt nytnytnytn gcngtntggg tnytnacngg ngarytntgg 60
ccnggngcng argcnmgngc ngcnccntay ggngtnmgny tntgyggnmg ngarttyath 120
mgngcngtna thttyacntg yggnggnwsn mgntggmgnm gnwsngayat hytngcncay 180
gargcnatgg gngayacntt yccngaygcn gaygcngayg argaywsnyt ngcnggngar 240
ytngaygarg cnatgggnws nwsngartgg ytngcnytna cnaarwsncc ncargcntty 300
taymgnggnm gnccnwsntg gcarggnacn ccnggngtny tnmgnggnws nmgngaygtn 360

ytngcnggny tnwsnwsnws ntgytgyaar tggggntgyw snaarwsnga rathwsnwsn 420
ytntgy 426

<210> 7
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide ZC9736

<400> 7
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<210> 8
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide ZC9740

<400> 8
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<210> 9
<211> 55
<212> DNA
<213> Artificial Sequence

<220>
<223> Exon 1 sense oligonucleotide primer

<400> 9
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<210> 10
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Exon 1 antisense oligonucleotide primer

<400> 10
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<210> 11
<211> 41
<212> DNA
<213> Artificial Sequence

<220>
<223> Exon 2 sense oligonucleotide primer

<400> 11
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<210> 12
<211> 52
<212> DNA
<213> Artificial Sequence

<220>
<223> Exon 2 antisense oligonucleotide primer

<400> 12
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<210> 13
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> conserved motif

<221> VARIANT
<222> (1)...(4)
<223> Xaa = Any Amino Acid

<400> 13
Arg Xaa Xaa Arg
1

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